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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,678	KAYED ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *181-183,187 and 189-206* is/are pending in the application.

4a) Of the above claim(s) *192 and 193* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *181-183,187,189-191 and 194-206* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of Claims

1. The amendments filed on 23 June 2009 have been entered into the record and have been fully considered. Claims 181, 187, 191, 194, and 203-206 are amended. Claims 184-186 and 188 have been cancelled.

2. Claims 181-183, 187, 189-191, 194-206, drawn to a composition comprising an isolated conformational epitope of an amyloid aggregate which forms in an animal or a human and which contributes to amyloid disease formation, are under consideration in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

3. Upon consideration of claim amendments, particularly to independent claim 181, thereby adding limitations of sequence identifier, support surface material, etc., the rejections under 35 U.S.C. 102 (a), (b) and (e) have been withdrawn.

4. Upon consideration of claim amendments, particularly to independent claim 181, the rejection under 35 U.S.C. 103 (a), has been withdrawn.

5. Objection maintained

Specification:

Applicant argues that the objected hyperlink on page 12, line 5, or on any other location in the document, could not be located.

Applicant's arguments have been considered, however, are not found to be persuasive. Please note the paragraph insert from page 12 of the specification showing the hyperlink:

> One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., J. Mol. Biol. 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for 5 Biotechnology Information **(http://www.ncbi.nlm.nih.gov/)**. Typically, default program parameters can be used to perform the sequence comparison, although customized parameters can also be used. For amino acid sequences, the BLASTP program uses as defaults a wordlength ON) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix, see for example, Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89,10915 (1989). Conservative substitutions involve substitutions between amino acids in the same class.

(emphasis added). Appropriate correction is required.

6. New Claim Objections

Claims 181 and 191 are objected to because of the following informalities:

i) Claim 181 recites non-elected inventions.

ii) Claim 191 has a typo on line 2 reciting "epitope comprises and epitope" (emphasis added).

Appropriate correction is required.

Applicant's response to earlier claim objection (claim 184)

(Please note that the currently amended claim 181 is objected on the same ground).

7. Applicant argues that the objection to nonelected species in the claim seems to "indicate that restriction to the elected species had been invoked". Applicant further states that a rejoinder of the sequence species would be appropriate because the combination of support surface materials and the sequences recited in the amended independent claim 181 is novel and unobvious irrespective of the amino acid sequence used.

8. Applicant's arguments are fully considered, however, are not found to be persuasive. As noted in the previous Office Action and reiterated below, the instant invention is prima facie obvious in view of the prior art teachings. Furthermore, Applicant's reference to the sequences as **species** is mistaken as the sequences are directed to separate **inventions** (page 4, para 4). As stated in the previous Office Action it is reiterated that:

The inventions listed as Groups A-I do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: In the instant case, the different inventions of Groups (A-I) are unique proteins of different lengths and are composed of different amino acids. Accordingly, each of the different protein sequences are not so linked under PCT Rule 13.1 and are thus placed in nine different inventive groups numbered A-I. Searching all of the sequences in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches. Furthermore, each of the sequences represents a different protein with unique and diverse functional features.

The requirement is still deemed proper and is therefore made FINAL.

New Rejections

Applicant's amendment necessitated the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 181-183, 189, 191, 195-206 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjernberg et al., in view of Garzon-Rodriguez et al. and Ingenito et al., and further in view of Braun; as evidenced by Goyal et al. and Wolf et al.

11. The claims are drawn to a composition comprising an isolated conformational epitope of an amyloid aggregate that forms in a human or animal and contributes to amyloid disease, wherein the composition comprises a peptide and the epitope is conformationally constrained on a curved/flat surface or on a surface of a particle on a support surface comprising a metal or mixtures thereof, e.g. gold or colloidal gold; is an Aβ amyloid epitope of SEQ ID NO: 2; and is a toxic species of an amyloid aggregate (claims 181-183, 191, 197-202). The claims also recite that the aggregate has a molecular weight of 1 kDa to about 100,000,000 kDa, and that the C-terminus of the peptide epitope is bound to the surface by a carboxy thiol linkage (claims 189, 195-196), wherein the surface is flat or comprises a pleated sheet or is a protein (claims 203-206).

12. Tjernberg et al. teach conformationally constrained peptides in solution comprising Aβ fragments necessary for aggregation and fibril formation (abstract; Introduction, para 1; page 345, col 2, para 1). The reference further teaches that the polymerization of the amyloid fibrils results in the pathogenesis of amyloid diseases like Alzheimer's Disease, therefore, is neurotoxic (page 349, col 1, para 4; Introduction, para 1). Since the amyloid peptides of the reference are purified during processing (page 345, col 2, para 1), the peptides are isolated by the definition in the instant specification that states that isolated means "purified, substantially purified or partially purified" (para 0046).

13. Tjernberg et al. do not teach that the C-terminal end of the amyloid peptide is bound to the surface by a carboxy thiol linkage.

14. Garzon-Rodriguez et al. teach that the carboxyl terminal residues of Aβ peptides constitute a richly hydrophobic domain that is associated with the cell membrane. The reference also teaches that the carboxyl terminal is critical for the assembly dynamics of amyloid. Still further Garzon-Rodriguez et al. teach that the amyloid fibril has a β pleated sheet structure (page 22645, Introduction). It is well established that the amyloid fibrils are formed by the sequential addition of Aβ subunits, thereby teaching that the amyloid peptides having epitopes for aggregate formation are bound to the amyloid fibril. It is further evidenced that the β- or A4 amyloid protein having 100% sequence homology with the instantly claimed SEQ ID NO: 2 (Goyal et al. abstract; see Appendix A for SCORE alignment) aggregates in the brain of AD patients. It is also well established in the literature that amyloid protein subunits associated with disease forming aggregates have a molecular weight of 4.2-4.5 kDa (Wolf et al. page 2079, para 1).

15. Ingenito et al. teach peptide synthesis by linking a thiol to generate peptide-C-terminal thioesters (abstract).

16. Tjernberg et al., Garzon-Rodriguez et al. or Ingenito et al. do not teach the surface specifications of a particle coated with a metal or gold.

17. Braun teaches the administration of pharmaceutical preparations or compositions comprising an antigen. Specifically, Braun teaches that the antigen is coated onto a surface of carrier particles of colloidal gold (para 0414). Since the particle is spherical (para 0431), it would inherently have a curved surface.

18. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the composition comprising conformationally constrained C-terminus peptides comprising Aβ fragments necessary for aggregation and fibril formation as taught by the combined teachings of Tjernburg et al., and Garzon-Rodriguez et al., by having a thiol linkage at the carboxyl end as taught by Ingenito et al., and by constraining onto colloidal gold particles in view of Braun. The person of ordinary skill in the art would have been motivated to link a thiol group, because the displacement with a suitable thiol at the C-terminus end produces peptide thioesters with much higher yields and is a reproducible method for the synthesis of proteins with backbone-engineered structure (Ingenito et al., page 11369, abstract; para 1). The person of ordinary skill in the art would have been further motivated to use gold for constraining the conformational epitopes of amyloid because gold provides uniformity of size in a range of particle sizes with suitable density, appropriate for intracellular delivery and reduced toxicity (Braun, para 0414-0415). The person of ordinary skill in the art would have expected success because peptide C-terminal thioesters have been successfully used for peptide synthesis in the prior art. Additionally, the synthesis of constrained conformational epitopes on gold surface was being performed in pharmaceutical and research laboratories, at the time the invention was made.

19. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

20. Claims 181-183, 187, 189-191, 194-195, 197-206, are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjernberg et al., in view of Garzon-Rodriguez et al. and Braun, and further in view of Nordstedt et al.

21. The claims further recite that the composition comprising an isolated conformational epitope of an amyloid aggregate is constrained on a flat surface wherein the composition or the epitope is chemically bound to the surface, and wherein the epitope comprises 5 or more monomers (claims 187, 190, and 194).

22. The teachings of Tjernberg et al, Garzon-Rodriguez et al. and Braun are set forth above.

23. Tjernberg et al., Garzon-Rodriguez et al. and Braun do not teach the surface specifications or that the amyloid comprises 5 or more monomers.

24. Nordstedt et al teach the synthesis of ten-mers corresponding to consecutive sequences of Aβ 1-40 on a filter matrix, wherein the peptides are coupled to cellulose membranes using 2 molecules of β alanine as spacer (col 5, lines 52-57), i.e. the peptides are chemically bound to the membrane.

25. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the composition comprising conformationally constrained peptides in solution comprising Aβ fragments necessary for aggregation and fibril formation in view of the combined teachings of Tjernburg et al., Garzon-Rodriguez et al. and Braun by making ten-mer amyloid aggregate coupled or constrained onto a membrane surface as taught

by Nordstedt et al. The person of ordinary skill in the art would have been motivated to have a composition comprising 5 or more monomers of amyloid peptide because the disease associated amyloid consists of thin fibrils of polymerized Aβ, and a rational pharmacological approach for the prevention of amyloidogenesis would involve interference with Aβ polymerization. The person of ordinary skill in the art would have expected success because synthesis of peptide or Aβ polymers chemically bound on flat membrane is a routine technique in pharmaceutical laboratories, and was being performed in pharmaceutical and research laboratories at the time the invention was made.

26. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Applicant's response

27. Applicant alleges that none of the prior art references cited in the rejections "taken alone or in combination, describes or renders obvious the invention recited in Applicants' presently amended claims". Moreover, Applicant indicates that "claim 184" "was not mentioned in the Office Action". Emphasizing on the current claim amendment, Applicant further directs the argument asserting that none of the references describes or suggests a composition as claimed in claim 181, because it "is novel and unobvious".

28. Applicant's arguments are fully considered, however, are not found to be persuasive. Although all previous rejections have been withdrawn pursuant to

current claim amendments, Applicant's arguments are being addressed to the extent that they are relevant to the new rejections. Contradictory to Applicant's allegation, claim 184 had been included in the obviousness rejections (see para 17, 24, and 38 of the last Office Action). Applicant has merely stated that the references neither describe nor suggest without substantiating the allegations. Therefore, for reasons described in the previous Office Action and reiterated above, the combined teachings of the references render the claimed invention as *prima facie* obvious.

Conclusion

29. No claims are allowed.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

31. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
25 October 2009

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649